

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 September 2003 (18.09.2003)

PCT

(10) International Publication Number
WO 03/075959 A1

- (51) International Patent Classification⁷: **A61K 45/06**,
A61P 35/00
- (21) International Application Number: PCT/EP03/02365
- (22) International Filing Date: 7 March 2003 (07.03.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0205537.4 8 March 2002 (08.03.2002) GB
0229054.2 12 December 2002 (12.12.2002) GB
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **NAKAJIMA, Motowo** [JP/JP]; 14-8-301, Asahigaoka-cho, Ashiya-shi, Hyogo Pref. 650-0012 (JP).
- (74) Agent: **GROS, Florent**; NOVARTIS AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **MATRIX METALLOPROTEINASE INHIBITORS IN COMBINATION WITH HYPOTHERMIA AND/OR RADIOTHERAPY FOR THE TREATMENT OF CANCER**

(57) Abstract: The invention provides a method of treating cancer in a subject in need of such treatment which comprises: radiotherapy, or cytotoxic therapy in combination with heat shock, and further comprises administering to the subject an effective amount of a matrix metalloproteinase.

WO 03/075959 A1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/02365

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 07697 A (PFIZER) 26 February 1998 (1998-02-26) claims 1,8-10 page 1, line 7-17 page 20, line 7-15	1-4,6-9
X	WO 00 38717 A (SEARLE) 6 July 2000 (2000-07-06) claims 1-3,18 page 1, line 6-11 page 8, line 27-32 page 12, line 12-18	1-4,6,7, 9
X	WO 99 21583 A (WARNER-LAMBERT) 6 May 1999 (1999-05-06) claims 1,6	1,3,4
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

26 June 2003

Date of mailing of the international search report

02/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/02365

G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M.HAQ E.A.: "Addition of matrix metalloproteinase inhibition to conventional cytotoxic therapy reduces tumor implantation and prolongs survival in a murine model of human pancreatic cancer" CANCER RESEARCH, vol. 60, no. 12, 2000, pages 3207-3211, XP001042323 page 3207 page 3209	1-4,6,7
X	--- A.L.THOMAS, W.P.STEWARD: "Marimastat: the clinical development of a matrix metalloproteinase inhibitor" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 9, no. 12, 2000, pages 2913-2922, XP008018598 page 2913 page 2917, column 2 page 2918	1-4,6,7, 9
X	--- L.JONES E.A.: "the matrix metalloproteinases and their inhibitors in the treatment of pancreatic cancer" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 880, 1999, pages 288-307, XP008018602 page 288 page 300	1-4,6,7, 9
X	--- YASUNOBU SAWAJI E.A.: "Transient increase of intracellular cAMP by heat shock initiates the suppression of MT1-MMP production of tumor cells" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES vol. 878, 1999, pages 707-709, XP008018601 page 707 -page 708 -----	1,3,4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1,2,6,7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02365

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/02365

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9807697	A	26-02-1998	AP 733 A	12-02-1999
			AU 711585 B2	14-10-1999
			AU 3456397 A	06-03-1998
			BG 103191 A	30-11-1999
			BR 9711223 A	17-08-1999
			CN 1228083 A	08-09-1999
			EP 0922030 A1	16-06-1999
			HR 970453 A1	31-08-1998
			WO 9807697 A1	26-02-1998
			JP 2000501423 T	08-02-2000
			NO 990821 A	23-02-1999
			PL 331895 A1	16-08-1999
			SK 21499 A3	16-05-2000
			TR 9900387 T2	21-04-1999
			TW 397823 B	11-07-2000
			US 6153609 A	28-11-2000
			ZA 9707561 A	22-02-1999
WO 0038717	A	06-07-2000	AU 2207000 A	31-07-2000
			AU 2209800 A	31-07-2000
			AU 2210400 A	31-07-2000
			AU 2380500 A	31-07-2000
			AU 2592600 A	31-07-2000
			AU 2593600 A	12-07-2000
			AU 2713400 A	31-07-2000
			AU 2713500 A	31-07-2000
			AU 2713600 A	31-07-2000
			BR 9916518 A	29-01-2002
			BR 9916536 A	02-01-2002
			BR 9916544 A	08-01-2002
			CA 2356302 A1	06-07-2000
			CA 2356402 A1	06-07-2000
			CA 2356426 A1	29-06-2000
			CA 2356459 A1	06-07-2000
			CA 2356462 A1	06-07-2000
			CA 2356547 A1	06-07-2000
			CA 2356606 A1	06-07-2000
			CA 2356748 A1	06-07-2000
			CA 2356929 A1	06-07-2000
			CN 1398189 T	19-02-2003
			CN 1346282 T	24-04-2002
			CN 1371286 T	25-09-2002
			CZ 20012320 A3	16-10-2002
			CZ 20012321 A3	16-10-2002
			EP 1140177 A2	10-10-2001
			EP 1140178 A2	10-10-2001
			EP 1140179 A2	10-10-2001
			EP 1140192 A2	10-10-2001
			EP 1140193 A2	10-10-2001
			EP 1140194 A2	10-10-2001
			EP 1140181 A1	10-10-2001
			EP 1140182 A2	10-10-2001
			EP 1140183 A1	10-10-2001
			HU 0104669 A2	29-05-2002
			HU 0104747 A2	29-04-2002
			HU 0104814 A2	29-04-2002
			JP 2002532563 T	02-10-2002
			JP 2002533387 T	08-10-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/02365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0038717	A	JP 2002533404 T	08-10-2002
		JP 2002535249 T	22-10-2002
		JP 2002533405 T	08-10-2002
		JP 2002533406 T	08-10-2002
		JP 2002533407 T	08-10-2002
		JP 2002533416 T	08-10-2002
		JP 2002533422 T	08-10-2002
WO 9921583	A	06-05-1999	
		AU 1110799 A	17-05-1999
		WO 9921583 A1	06-05-1999
		ZA 9809840 A	05-05-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

BEST AVAILABLE COPY